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EXAMINER	
FOSTER, CHRISTINE E	
ART UNIT	PAPER NUMBER
1641	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/777,683	MOSS ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☒ Claim(s) *7,8,14 and 15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-16 in the reply filed on 10/19/06 is acknowledged. The election of the species of *two-antibody sandwich-type assay* and of *diagnosis* is further acknowledged. Applicant's reply states that claims 1-6, 8-13, and 15-16 read on the elected species.

2. Because a search of claims 7 and 14 could be performed without undue burden, the requirement for restriction between the species of Assay Formats (see p. 3 of the previous Office action) is withdrawn, and claims 7 and 14 are examined below.

3. Claims 17-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/19/06.

4. Claims 1-18 are pending in the application, with claims 17-18 currently withdrawn. Claims 1-16 are subject to examination below.

Priority

5. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Specifically, it is noted that the transmittal letter and the oath refer to provisional application No. 60/447,310, filed 02/14/2003. However, Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

6. If applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 1119(e), **a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet**. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications.

If the instant application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under

37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Information Disclosure Statement

7. An Information Disclosure Statement (IDS) has not been received. The Examiner notes that submission of an IDS is not required, but reminds Applicant of the duty to disclose information material to patentability (see 37 CFR 1.56).

Specification

8. The use of the trademark "TWEEN" has been noted in this application (see p. 28-29). It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

9. Claims 7-8 and 14-15 objected to because of the following informalities:

10. Claims 8 and 15 recite "a step of bringing into mutual contact the following three components; **i.e.,** a solid phase..."), which is objected to because the term "i.e." appears to be unnecessary in the claim. The examiner would suggest as an alternative the following: "...the following three components: a solid phase...".

11. Claims 7-8 and 14-15 also refer to "a sample", which appears to refer back to "the biological sample" recited in claims 1 and 2, respectively. The examiner would suggest that the dependent claims refer to "the sample" or "said sample" in order to make clear that the same sample previously mentioned is being used.

12. Claims 8 and 15 are also objected to because they refer to a "first antibody immobilized onto a solid phase – CAP 18 – second antibody". It is not clear why the text appears in quotation marks in the claims. Correction and/or clarification are requested.

13. Similarly, claims 7 and 14 refer to "an antibody capable of binding to a peptide having an amino acid sequence of SEQ ID NO:1," which appears in quotation marks in the claims.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The elected invention is drawn to a method for the diagnosis of cystic fibrosis based by measuring the level of "CAP 18".

Applicant has defined "CAP 18" so as to encompass "proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc." (p. 7, the last full paragraph).

As such, the claims are drawn to methods of diagnosis based on the measurement of a large genus of proteins that differ structurally from native CAP 18, but which do not differ significantly in function. This genus would include, for example, proteins having deletions, additions, or substitutions to the native CAP 18 amino acid sequence (including fusion proteins), post-translational modifications, chemical modifications, etc. However, in describing only measurement of the native CAP 18 protein, the specification does not provide a written description to support evidence of possession of the genus of "proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc.".

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter

later claimed. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." MPEP 2163.

Although drawn to the DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co. The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, or chemical name', of the claimed subject matter sufficient to distinguish it from other materials." Id. at 1567, 43 USPQ2d at 1405. The court also stated that:

> a generic statement such as "vertebrate insulin CDNA" or "mammalian insulin CDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. at 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAS might be described. "A description of a genus of cDNAS may be achieved by means of a recitation of a representative number of cDNAS, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem. Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics; i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. at 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

Although the inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of the genus of "proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc.", per Lilly by structurally describing representative structural analogs or by describing "structural features

common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

However, the instant specification does not describe the genus of "proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc." in a manner that satisfies either the Lilly or Enzo standards. Although the specification discloses human CAP 18 (SEQ ID NO:4, see p. 7), it does not disclose what portions of this protein are responsible for function or behavior, and therefore does not disclose what "slight structural differences" would retain physiological function. The specification does not describe what types of structural differences would be encompassed, what structural features are shared among members of the genus, or provide detailed characteristics to identify the members of the genus. As such, one skilled in the art cannot readily envision the structure of the proteins to be measured. Furthermore, the specification does not provide any correlation between any common structure and function (i.e., "intravital function".

Since the specification fails to adequately describe the genus of "proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc.", it also fails to adequately describe the method in which such proteins are measured and used in diagnosis of cystic fibrosis.

For example, the specification also discloses art-recognized methods for producing antibodies by immunizing animals with peptide portions of human CAP 18 (see p. 9-13). However, the specification fails to disclose any examples of "proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc.", and fails to specifically identify what portions of this protein are responsible for binding to antibodies.

It is known in the art that minor changes to a protein sequence can abolish antibody binding (see enablement rejection below). Applicant has not disclosed what "slight structural differences" may be made without altering an antibody epitope, and has provided written description only for antibodies raised against the native human CAP 18 protein sequence. Applicant therefore has not described how to measure CAP 18 proteins that are structurally different from the native human CAP 18 protein. One skilled in the art would not envisage possession of the currently claimed methods of detection of the genus of CAP 18 proteins using antibodies raised against the native human CAP 18 sequence.

Moreover, the prior art teaches that CAP 18 proteins from different species differ in amino acid sequence. Such non-human CAP 18 proteins are also encompassed by the claims. Larrick et al. ("Human CAP18: a Novel Antimicrobial Lipopolysaccharide-Binding Protein" *Infection and Immunity* 63 (1995), 1291-1297) teach that the amino acid sequences of pig and rabbit CAP 18 family members share only about 60% identity with the human sequence (see Figure 2 and Table 1). As discussed above, it is known that a single amino acid change can abolish an antibody epitope. As such, one skilled in the art would not envisage possession of detection and diagnosis of all CAP 18-related proteins in all animal species, given that antibodies

raised against the human sequence would not reasonably be expected to recognize CAP 18 proteins from other species, which differ significantly in protein sequence from the human protein.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

16. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed methods relate to the assessment of cystic fibrosis based on measurements of levels of "CAP 18". The application has been considered below with respect to the currently elected species of **diagnosis** of cystic fibrosis as the type of assessment.

The nature of the invention relates to the investigation of levels of human CAP 18 protein in bronchoalveolar lavage fluid (BALF) and expectoration samples in human subjects suffering from cystic fibrosis as compared to healthy human control subjects (see especially p. 27-28). The specification discloses measuring CAP 18 levels by use of antibodies raised against the human CAP 18 protein (SEQ ID NO:4; see p. 7 and p. 25, "Production of polyclonal antibody") and/or against partial peptide portions of the human CAP 18 protein, namely SEQ ID NO:1, 2, or 3 (see especially p. 9-10, 18 and 24-25).

However, as discussed above with respect to the written description requirement, Applicant has defined "CAP 18" so as to encompass "proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc." (p. 7, the last full paragraph). Thus, the claims are not limited to detection of the native human CAP 18 protein (SEQ ID NO:4).

As such, the claims are broadly drawn to methods of diagnosis based on the measurement of a genus of proteins that differ structurally from native CAP 18, but which do not differ significantly in function. This genus would include, for example, proteins having deletions, additions, or substitutions to the native CAP 18 amino acid sequence (including fusion proteins), post-translational modifications, chemical modifications, etc., as well as CAP 18 proteins from all species.

The specification does not provide sufficient enabling description of the claimed invention for the following reasons.

First, it is noted that the specification guides the skilled artisan to diagnose cystic fibrosis based on elevated levels of CAP 18 as compared to healthy controls (see especially p. 21). However, it is known that CAP 18 is elevated in various disease conditions that are unrelated to cystic fibrosis. For example, Applicant's own postfiling work teaches that CAP 18 is elevated in both cystic fibrosis as well as in COPD, and is elevated to comparable levels in both diseases (79.6 ± 93 vs. 75.3 ± 38.9 ng/ml, respectively) (Xiao et al., "Sputum Cathelicidin, Urokinase, Plasminogen Activation System Components, and Cytokines Discriminate Cystic Fibrosis, COPD, and Asthma Inflammation" (2005) *Chest* 128;2316-2326, in particular the abstract and p. 2319-2320, "CAP18 in Serum, BAL Fluid, and Sputum"). Applicant's work in copending

application 2006/0057134 A1 (Kirikae et al.) also discloses that CAP 18 is markedly elevated in sputum in bacterial pneumonia patients as compared to controls, such that it can be used to diagnose this disease (see especially paragraphs 196-209, 238-242, and claims 25-32). In addition, Schaller-Bals et al. ("Increased Levels of Antimicrobial Peptides in Tracheal Aspirates of Newborn Infants during Infection" *Am J. Respir Crit Care Med* **165** (2002), p. 992-995) teach that CAP 18 ("LL-37/hCAP-18") is elevated in infection and inflammation in newborns (see in particular the abstract).

The instant specification fails to provide any guidance with regard to differential diagnosis—i.e., how cystic fibrosis may be diagnosed based on elevated CAP 18 levels alone, given that it is known that CAP 18 is elevated in a number of different diseases, and therefore is not specific to cystic fibrosis. Rather, all of the examples in the specification relate to subjects whose disease condition was already known, i.e., those subjects who were already diagnosed with the disease. As a result, one skilled in the art would not know, upon obtaining a finding of elevated CAP 18 levels in a subject, whether to diagnose a subject with cystic fibrosis, COPD, bacterial pneumonia, or infection and inflammation.

Furthermore, in describing only measurement of the native human CAP 18 protein, the specification does not enable one skilled in the art to detect the genus of "proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc.". The specification discloses only the human CAP 18 protein with the amino acid sequence of SEQ ID NO:4, as well as the partial peptides thereof SEQ ID NO:1-3. However, the claims are open-ended given the definition of "CAP 18" in the specification; it expands the detected "CAP 18" proteins so to include additions,

truncations, substitutions, as well as other types of modifications to the sequence shown in SEQ ID NO:4.

The prior art teaches that antibodies raised against the native CAP 18 protein would not reasonably be expected to be reactive with "proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc.". For example, Lederman et al. (Molecular Immunology (1991) 28: 1171-1181, see entire document) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody. Further, Li et al. (PNAS 1980. 77: 3211-3214, see entire document) in the context of constructing analogs, disclose that immunoreactivity is dissociated from other biological activities. Similarly, Colman et al. (Research in Immunology, 1994; 145(1): 33-36) teach that single amino acid changes in an antigen can effectively abolish antibody antigen binding (see entire document, particularly page 34). Abaza et al. (Journal of Protein Chemistry, Vol. 11, No. 5, 1992, pages 433-444) also teach that single amino acid substitutions outside the antigenic site on a protein effect antibody binding (see entire document, particularly Results on pages 435-436).

The specification discloses that "CAP 18" may be detected through use of an antibody capable of specific binding to CAP 18 (p. 8). However, in describing only antibodies raised against the known sequence of native human CAP 18, the specification does not provide a sufficient enabling description of an antibody reactive towards the genus of "proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc.". Therefore, the specification does not teach the skilled artisan how to predictably measure "proteins having slight structural differences

from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc." or to employ such measurements for diagnosis, given that antibodies raised against the native CAP 18 protein would not reasonably be expected to bind to such structural analogs.

It is further noted that the claims are not limited with respect to the source of the biological sample; rather, the specification indicates that any mammalian subject can be used to provide a source of sample (see p. 7), such that the claims encompass diagnosis of any "animal which may possibly suffer from CF". However, the guidance presented in the specification relate only to the measurement of human CAP 18; in particular, the data presented only relate to the investigation of CAP 18 levels in humans with cystic fibrosis.

Furthermore, as noted above, the prior art teaches that CAP 18 proteins from different species differ in amino acid sequence. Larrick et al. (discussed above) teach that the amino acid sequences of pig and rabbit CAP 18 family members share only about 60% identity with the human sequence (see especially Figure 2 and Table 1). Given that a single amino acid change may abolish antibody binding, the specification fails to teach the skilled artisan how to predictably use antibodies raised against the human sequence in order to measure CAP 18 proteins in all other species, which may differ much more dramatically in amino acid sequence than by a single amino acid.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as

originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling." Given that it is apparently not even known whether CAP 18 even exists and is present in all mammalian species, the specification fails to teach the skilled artisan how to detect CAP 18 in all mammals and carry out diagnosis of cystic fibrosis therefrom.

The claims are also broad with respect to the type of biological sample, as the specification indicates that any type of biological sample may be employed, e.g. any type of excretion (see p. 6). However, the data presented for BALF and expectoration samples do not reasonably correlate with this claim scope. Applicant's own postfiling work teaches that serum levels of CAP 18 were similar in subjects with cystic fibrosis as compared to healthy controls (see Xiao et al., especially p. 2319, right column, the last paragraph, and p. 2324, right column, the last paragraph). In this light, it is clear that the specification does not teach how to employ all types of samples to diagnose cystic fibrosis based on levels of CAP 18, given that serum CAP 18 levels are no different in healthy vs. disease populations and therefore could not be successfully used in the claimed methods.

It is further noted that the claims are broad with respect to how CAP 18 levels are to be correlated with cystic fibrosis, and do not recite, for example, whether high or low levels would be indicative of the disease state. The specification provides support only for diagnosis of cystic fibrosis based on higher CAP 18 levels as compared to healthy controls (see p. 21), and therefore fails to teach the skilled artisan how to carry out diagnosis when the levels are the same or depressed as compared to those in healthy controls.

In summary, it is known that CAP 18 is not a specific marker of cystic fibrosis, but rather is elevated in various unrelated conditions, yet the specification does not provide guidance in regard to differential diagnosis, and therefore fails to teach the skilled artisan how to predictably diagnose cystic fibrosis based on CAP 18 levels. The prior art also establishes that CAP 18 proteins differ significantly in amino acid sequence among different species, and further that minor changes to a protein sequence can abolish antibody binding, which speaks to the unpredictability in using antibodies raised against one protein sequence to detect a distinct protein. Taken together with the lack of direction/guidance presented in the specification regarding detection of all CAP 18 proteins or structural analogs thereof and in all sample types (as well as the diagnosis of cystic fibrosis thereby), and the lack of working examples directed to same, and the breadth of the claims, the specification fails to teach the skilled artisan how to make and use the claimed invention without undue experimentation.

17. Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

18. Independent claims 1 and 2 recite measuring the level of "CAP 18", which is indefinite because the specification defines "CAP 18" so as to encompass **"proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc."** (p. 7, the last full paragraph).

However, it is noted that the above definition of "CAP 18" is open-ended, i.e. not limiting, and the specification does not provide a standard for ascertaining the scope of the claim since. The claims are clearly not limited to detection of native CAP 18; however, the specification does not define or clearly exemplify what proteins would be encompassed by this definition. It is not clear what types of structural differences or modifications, and also what *extent* of modification, would be encompassed by the claim. For example, would proteins differing by 1 or 10 amino acids from the native CAP 18 protein be considered to be "slightly different"? Homologs from other species? The specification does not define or provide a standard for understanding what would be considered to be a "slight structural difference". Because of this way that "CAP 18" is currently defined in the instant specification, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Furthermore, the use of the designation "CAP 18" alone to describe a particular protein renders the claim indefinite because different laboratories may use the same laboratory designation to define completely distinct proteins or protein fragments. This is true in the case of "CAP 18": the specification states that the entire amino acid sequence of human CAP 18 is given as SEQ ID NO:4 (see p. 7), which is a 170-amino acid protein. However, Montelaro et al. (US 6,835,713 B2) describe human CAP 18 (hCAP18) as being a 37-amino acid peptide (see column 1, lines 57-61). By contrast, Applicant's postfiling work (Xiao et al., discussed above) identifies

human CAP18 as an 140-amino acid protein (see p. 2317, left column, the first paragraph). As such, it is not clear what protein sequence is being detected since the claim refers only to "CAP 18" but does not adequately identify the species to be detected. Amendment of the claims to recite the SEQ ID NO may obviate this aspect of the rejection.

For all of the above reasons, the metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. Claims 1-7 and 10-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Bals et al. ("Salt-Independent Abnormality of Antimicrobial Activity in Cystic Fibrosis Airway Surface Fluid" *Am. J. Respir. Cell Mol. Biol.* **25** (2001), p. 21-25) and in light of the evidence of iHOP (Information Hyperlinked over Proteins – data for CAMP, cathelicidin antimicrobial peptide, p. 1, downloaded from http://www.ihop-net.org/UniPub/iHOP/gs/86912.html on 01/04/2007) and Larrick et al. ("Human CAP18: a Novel Antimicrobial Lipopolysaccharide-Binding Protein" *Infection and Immunity* 63 91995), 1291-1297)

Bals et al. teach measuring the level of CAP 18 ("LL-37/hCAP-18") in a biological sample (bronchoalveolar lavage fluid and human bronchial xenografts generated from respiratory epithelial cells) and correlating the measurement with cystic fibrosis (see the entire document, in particular the abstract; p. 21, right column; p. 22, left column; Figures 3-4; and p. 23-24,

"Concentrations of Known Antimicrobial Peptides Are Equivalent in CF and Normal ASF"). Specifically, the reference teaches comparing CAP 18 levels in cystic fibrosis and healthy control subjects (Figure 4), which reads on the claimed correlation step as recited in claims 1-2.

The protein detected by Bals et al. (LL-37/hCAP-18) anticipates the claim limitation of being "CAP 18" in light of the evidence of iHOP, which teaches that hCAP-18, CAP-18, and LL37 are synonyms that designate the same protein (p. 1, top right).

With respect to claims 4, and 11, the measurement of CAP18 was via antigen-antibody reaction using polyclonal antisera (se p. 21, right column, "Preparation of Antibodies..." and p. 22, left column, "Determination of Peptide Concentrations...").

With respect to claims 5 and 12, the antibody of Bals et al. was raised against LL-37/hCAP-18 containing the C-terminal 37 amino acids (see p. 21, right column, "Preparation of Antibodies..."). Larrick et al. provide evidence that this peptide has "an amino acid sequence of SEQ ID NO:1" as claimed, in that (for example) it includes the amino acid sequence "Lys—Glu" at position 115-116 (see Figure 2, the sequence provided for "Human"). As such, the antibody of Bals et al. meets the limitation of being capable of binding to a peptide having an amino acid sequence of SEQ ID NO:1 because as reflected by Applicant's sequence listing, SEQ ID NO:1 also includes the "Lys—Glu sequence at positions 5-6 and also 10-11 (see the sequence listing filed 9/20/04).

With respect to claims 6-7 and 13-14, Bals et al. teach bringing the sample into contact with a solid phase (nitrocellulose membrane) so as to immobilize the CAP 18, adding the polyclonal antibody specific for CAP 18 to form a complex, and detecting the complex using a

secondary peroxidase-labeled antibody (p. 22, left column, "Determination of Peptide Concentration..." and Figure 4).

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

23. Claims 8 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bals et al. in light of iHOP and Larrick, and in view of Weinberg et al. (US 6,187,536 B1).

Bals et al. is as discussed above, which teaches methods for measuring CAP 18 by dot-blot and immunoblot assay. However, the reference fails to specifically teach measuring CAP 18 using a sandwich-type, two-antibody immunoassay as recited.

However, such immunoassay formats were well known in the art at the time of the invention; for example, Weinberg et al. teach immunoassays comprising the steps of bringing

into contact a solid phase support in which a first anti-protein antibody is immobilized with a test sample to form a complex or "sandwich" (see column 21, line 44 to column 22, line 7). Subsequently, the complex is detected either via a detectable second antibody or a third detectable antibody. Weinberg et al. teach that in contrast with simple immunoassays such as dot blot or Western blot, "two-site" or "sandwich" assays as detailed above provide excellent results and can be made quantitative.

Therefore, it would have been obvious to one of ordinary skill in the art to employ the sandwich immunoassay format taught by Weinberg et al., using two CAP 18-specific antibodies, in order to measure CAP 18 in the method of Bals et al. because Weinberg et al. teach that such immunoassays provide excellent results as compared with simple dot blot or Western blot assays, which are the methods used in Bals et al.

Conclusion

24. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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